Transcriptomic profiling of non-ischemic cardiomyopathies; what lies beyond sarcomere in characterization of non-ischemic cardiomyopathies?

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Background: The application of unbiased omics to discover the molecular basis of non-ischemic cardiomyopathies (NICM) advances our understanding of the pathogenesis of idiopathic cardiomyopathies and opens a new avenue for targeted personalized drug development.

Methods: We performed a post-hoc analysis on the high throughput gene expression database of the Myocardial Applied Genomics Network that was obtained from the repository site at the University of Pennsylvania. Samples were collected at the time of heart transplantation from left ventricular tissues of 36 non-failing (NF) donors, 38 individuals with dilated cardiomyopathy (DCM), and 27 individuals with hypertrophic cardiomyopathy (HCM). Samples were processed for RNA isolation, library preparation, and next-generation sequencing. After quality control, differential gene expression (DEG), and pathway analysis were performed. Whole transcriptomic profiles of DCM and HCM were compared with NF controls.

Results: A total of 101participants (48% female) with median age of 50 years (ranged 21-80 years) were included in the analysis. Participants were age- and sex-matched between DCM, HCM, and NF groups. African Americans comprised 41% of the total study population. With log [fold change] greater than 2, and $p<0.01$, we identified 118 DEGs in DCM vs NF and 84 DEGs in HCM vs NF. More than 50% of these DEGs being overlapping between DCM and HCM. Mutual up-regulated genes in DCN and HCM encoded globin proteins, extracellular matrix glycoproteins, proteins involved in angiogenesis, calcium cycling, and natriuretic peptides. Unique upregulated DEGs in HCM were related to growth factors, glucose metabolism, transmembrane proteins involved in NOTCH signaling, and active transportation. Unique upregulated DEGs in DCM were related to the innate immune system and ion transportation. DCM and HCM shared more similarities in terms of downregulated DEG profile including pathways of several tubulin class proteins, oxidoreductase class, and scaffold/adaptor proteins.

Conclusion: DCM and HCM have several similarities at the transcriptomics level including biomarkers of cardiomyocyte senescence. Biomarkers of metabolism and fibrosis were more dysregulated in HCM, while innate immune response dysregulation was more prominent in DCM.

Figure1, Overall study design and main results, A) Study workflow, B) Differential gene expression of dilated cardiomyopathy (DCM) compared to non-failing (NF), C) Differential gene expression of hypertrophic cardiomyopathy (HCM) compared to non-failing (NF)

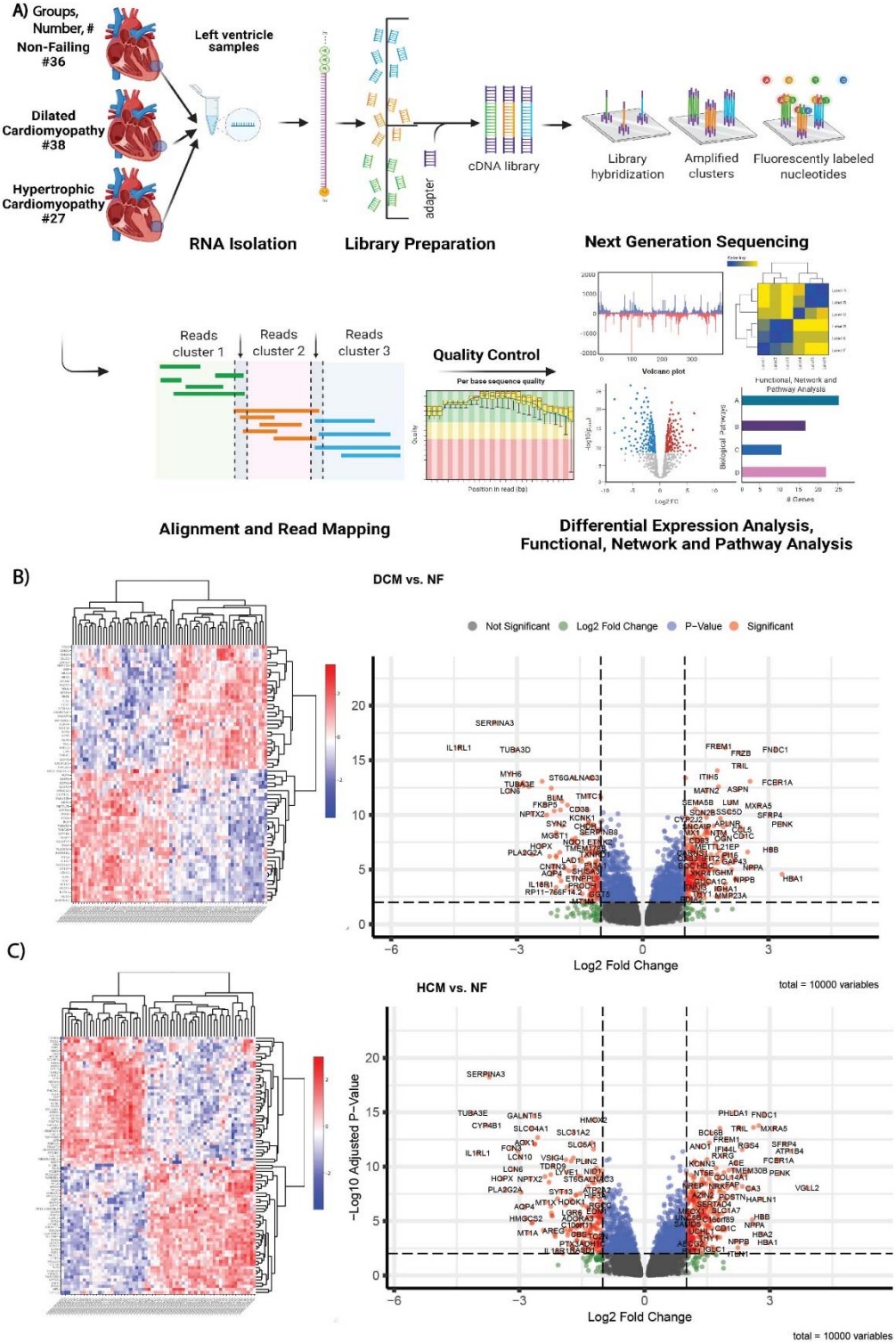

Table1. List of genes that mutually or uniquely expressed differently in patients with hypertrophic cardiomyopathy vs dilated cardiomyopathy

Up Regulated Genes			**Down Regulated Genes**		
Mutual	**Unique to DCM**	**Unique to HCM**	**Mutual**	**Unique to DCM**	**Unique to HCM**
SFRP4	*COL22A1*	*VGLL2*	*TUBA3E*	*RP11-216L13.16*	*DHRS7C*
PENK	*SEZ6L*	*ATP1B4*	*IL1RL1*	*LBP*	*MT1M*
FCER1A	*CXCL10*	*CA3*	*SERPINA3*	*SAA2*	*MT1X*
CRISPLD1	*LAMP5*	*SYTL5*	*CYP4B1*	*RNASE2*	*TMIGD3*
MXRA5	*CAPN6*	*TMEM30B*	*TUBA3D*	*ALOX15B*	*RP11-1081M5.3*
HBA1	*CXCL11*	*F2RL2*	*HOPX*	*LGI3*	*VSIG4*
FNDC1	*CLC*	*RGS4*	*PLA2G2A*	*CYP4Z1*	*TDRD9*
HBA2	*GZMH*	*GDF6*	*FCN3*	*CYP4Z2P*	*FCGBP*
HBB	*FHAD1*	*HTR2B*	*LCN6*	*MCEMP1*	*HPR*
HAPLN1	*APCDD1L*	*THBS4*	*MYH6*	*NMRAL1P1*	*PSPHP1*
FRZB	*LEFTY2*	*DIO2*	*LCN10*	*CD177*	*SYT13*
NPPA	*ARMS2*	*ITLN1*	*SCGN*	*GMNC*	*PSPHP1*
ASPN	*CCL4L2*	*MINOS1-NBL1*	*AQP4*	*TCF24*	*SYT13*
CENPA	*ESM1*	*ACE*	*GALNT15*	*CNTN3*	
ANKRD34C	*IGLV2-11*	*SCUBE2*	*AOX1*	*C1orf105*	
LUM	*AGTR2*	*SOX7*	*HMGCS2*	*PGA4*	
TRIL	*FATE1*	*PHLDA1*	*MT1A*	*CMTM5*	
NPPB	*HNRNPA1P66*	*FAP*	*NPTX2*	*METTL7B*	
DNAAF3	*AQP10*	*POSTN*	*SLCO4A1*	*OVCH1*	
APLNR	*CD1C*	*COL14A1*	*IL1R2*	*METTL7B*	
	TRBC1	*TGFB2*	*FKBP5*	*OVCH1*	
	CCL5	*COL14A1*	*CD163*		
	CMA1	*TGFB2*	*SGPP2*		
	COL9A1		*BLM*		
	LYPD1		*SYN2*		
	TNMD		*MGST1*		
	CX3CR1		*FAM155B*		
	GLIS1		*RARRES1*		
	IGLC1		*GNMT*		
	IGHG2		*AREG*		
	SLAMF7		*PI15*		

	IGHG1		*IL18R1*
	GAP43		*PI15*
	OASL		*IL18R1*
	TBX21		
	MKRN2OS		
	UBD		
	ITGAL		
	KCNK17		
	ZNF365		
	GFRA3		
	PI16		
	BIRC7		
	SSC5D		
	CCL3L3		
	APOA1		
	GZMA		

(Log 2 [fold change] >2, and p<0.01 was considered significant. Genes listed per magnitude of log fold change)

Figure 2. Principal component analysis of transcriptomic profile of hypertrophic cardiomyopathy compared to dilated cardiomyopathy